EDITORIAL COMMENT

A Bigger Look Into the "Therapeutic Window" of Platelet Reactivity to Adenosine Diphosphate*

Udaya S. Tantry, PhD, Paul A. Gurbel, MD

A decade ago, small observational studies using light transmittance aggregometry suggested that post-stenting ischemic event occurrences were not linearly related to on-treatment platelet reactivity (OPR) levels but instead largely occurred above a moderate threshold level (1,2). For example, in the CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial) study of 20 patients with previous stent thrombosis (ST) and 100 age-matched patients without ST, >40% maximal platelet aggregation in response 20 μM adenosine diphosphate (ADP) was associated with ST (3). Subsequently, a number of studies using various platelet function assays including the most widely used VerifyNow P2Y12 assay demonstrated similar OPR cutoff values associated post-stenting ischemic event occurrences and termed an upper cut-off value as high OPR (HPR) (4). It was hypothesized that adequate protection against ischemic events with antiplatelet therapy is achieved by low to moderate levels of OPR in the majority of patients, whereas markedly low levels of OPR are associated with greatly increased bleeding risks, a so-called therapeutic window of $P2Y_{12}$ receptor reactivity during dual antiplatelet therapy with a $P2Y_{12}$ receptor inhibitor and aspirin, similar to the international normalized ratio for warfarin therapy (5,6).

How far has this translational research field advanced since then? Recent prospective, randomized trials of personalized antiplatelet therapy have failed to demonstrate the benefit of platelet function testing in improving outcomes in patients with HPR (7,8). It should be acknowledged that these trials are associated with major limitations, such as the enrollment of low-risk patients, which resulted in low event rates and lack of power and the use of high-dose clopidogrel, which is not an optimal strategy to overcome HPR and to improve clinical outcomes. In the ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) study, a multinational prospective registry of 8,582 patients (~50% of patients with acute coronary syndrome), HPR defined as >208 P2Y12 reaction units (PRUs) was independently associated with an ~2-fold increased risk of 2-year definite/probable ST (hazard ratio [HR]: 1.84, p = 0.009) and inversely correlated with major bleeding (HR: 0.82, p = 0.02), with a trend toward all-cause death

(HR: 1.27, p = 0.06) (9). In this issue of *JACC: Cardiovascular Interventions*, Kirtane et al. (10) further analyzed ADAPT-DES platelet reactivity data categorized in quintiles (a continuous variable rather than dichotomous variable that was done with HPR) in relation to clinical outcomes. They found that PRUs were associated in a monotonic fashion with ST and that ST was independently associated with the highest PRU quintile. The clinically relevant bleeding was independently associated with lowest PRU quintile, and bleeding events were equally distributed among other quintiles. Finally, all-cause mortality was only

associated with a higher PRU quintile in an unadjusted analysis.

The observations of Kirtane et al. in the largest dataset of platelet reactivity thus far reinforce what was observed in smaller studies a decade ago. It was demonstrated that the HPR cutoff values have high negative predictive value for thrombotic event occurrence, but the positive predictive value is low (4). The latter is due to very low thrombotic event rate and although HPR is a major determinant of the thrombotic event occurrences, clinical events are dependent on multiple factors in addition to HPR. Therefore, HPR may not be a standalone risk factor, but should be part of risk algorithm along with makers akin to CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) bleeding score or GRACE (Global Registry of Acute Coronary Events) risk score to improve risk prediction and facilitate personalization of antiplatelet therapy.

Unlike a strong and "monotonically increasing" relationship between platelet reactivity and stent thrombosis, clinically relevant bleeding was independently associated with the lowest quintile of PRU only. The latter is not surprising. The underlying mechanisms of bleeding are more complex and heterogeneous in origin, unlike coronary thrombotic events. Second, it is likely that only a very high level of platelet inhibition *appears to reliably influence* primary hemostasis. Earlier studies with glycoprotein IIb/IIIa antagonist (abciximab) demonstrated that bleeding time was affected only with 90% receptor blockade. Even with ~80% receptor blockade, a degree associated with significant inhibition of platelet aggregation, the bleeding time was only mildly affected (11). The results of the current analysis of ADAPT-DES are in line with the latter study and early results of other smaller studies (12).

Finally, the absence of an independent relationship between higher PRU and mortality is not surprising. The latter observation is similar to the finding of TRILOGY ACS (A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome Subjects) platelet function substudy (13). Multiple risk factors and covariates such as diabetes, old age, previous myocardial infarction, renal insufficiency, and smoking status may influence mortality by their effect on platelet physiology and thereby could have masked the independent association. In fact, univariate associations may be more important for the treating physician who is unable to adjust test results for multiple variables at the bedside (13).

Kirtane et al. (10) provide much more robust evidence of the "therapeutic widow" concept of platelet reactivity. However, only a large prospective personalized therapy trial that demonstrates improved outcomes when patients are within the window will advance this interesting field and silence the queries about whether HPR is a modifiable risk factor.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Paul A. Gurbel, Inova Center for Thrombosis Research and Drug Development, Inova Heart and Vascular Institute, 3600 Gallows Road, Fairfax, Virginia 22042. E-mail: pgurbel@lifebridgehealth.org.

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